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13. ABSTRACT (Maximum 200 words) The synthesis of a series of diazatrithia-15-crown-5 and diazatrithia-16-crown-5 ligands containing two 8-hydroxyquinoline side arms are reported. The ligands were prepared by a two-step process. First, diazatrithiacrown ethers 11 and 12 were prepared by treating bis(α -chloroamide) 5 with various dimercaptans followed by reduction using a boron-THF complex. Hydroxymethyl-substituted macrocycle 12 was rearranged to hydroxy-substituted diazatrithia-16-crown-5 in refluxing aqueous HCl. Macrocyclic diamines 11-13 were converted to either 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted diazatrithiacrown ethers 14-16 by a Mannich aminomethylation reaction or to 8-hydroxyquinolin-2-ylmethyl-substituted diazatrithiacrown ethers 17-19 by reductive amination using 8-hydroxyquinoline-2-carboxaldehyde.				
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15-Crown-5 and Diazatrithia-16-Crown-5 Ligands**

by

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Synthesis of Bis-8-Hydroxyquinoline-Armed Diazatrithia-15-Crown-5 and Diazatrithia-16-Crown-5 Ligands

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Results and Discussion

Synthesis of Diazatrithia Crown Ethers. Secondary ring nitrogen atoms in crown ethers offer a convenient site for attachment of alkyl substituents. The crab-like synthesis of diazacrown ethers using the bis(α -chloroacetamide)s provides a relatively high yield method to form macrocycles containing two secondary amine functions.^{1b,2} In this regard, bis(α -chloroamide) **5** was treated with various dimercaptans in MeCN using a carbonate base to form macrocyclic diazatrithiadiamides **6-8** in good yields (Scheme 1). As expected, the larger 2:2 cycloaddition products, macrocyclic tetraamides **9** and **10**, were also isolated in two cases in small yields. The NMR spectra of **9** and **10** were similar to those of **6** and **8**, respectively. High dilution techniques helped minimize the production of these undesired by-products. Macrocyclic diazatrithia ligands **11** and **12** were prepared by reducing macrocyclic diamides **6** and **8**, respectively, using a borane-THF complex. Initially, work up of the borane reduction products was done in refluxing 6 M HCl, but this process caused the formation of unexpected rearrangement and ring opened products as discussed below. Exposure to 6 M HCl at room temperature for a period of 10 minutes, along with extraction, was adequate for freeing the desired product from boron giving diazatrithia-18-crown-6 (**11**) and hydroxymethyl-substituted diazatrithia-15-crown-5 (**12**) in good yields.

The rearrangement product of **12** proved to be a new hydroxy-substituted diazatrithia-16-crown-5 (**13**) (Scheme 2). Ligand **13** is also of value in our research program. In an acid environment with heating, the protonated primary hydroxyl group from **12** becomes a leaving group when attacked by the neighboring ring sulfur atom. This leads to a charged epithio intermediate that is in turn attacked by water at the carbon atom most able to support a positive charge, forming **13**. A minor product from this reaction resulted from the intramolecular attack by a neighboring ring nitrogen atom forming **13a** in a very low-yield. A trace amount of another compound which has very similar properties to those of **13a** was also observed. This material could be a result of the attack of the other ring nitrogen atom on the epithio intermediate.

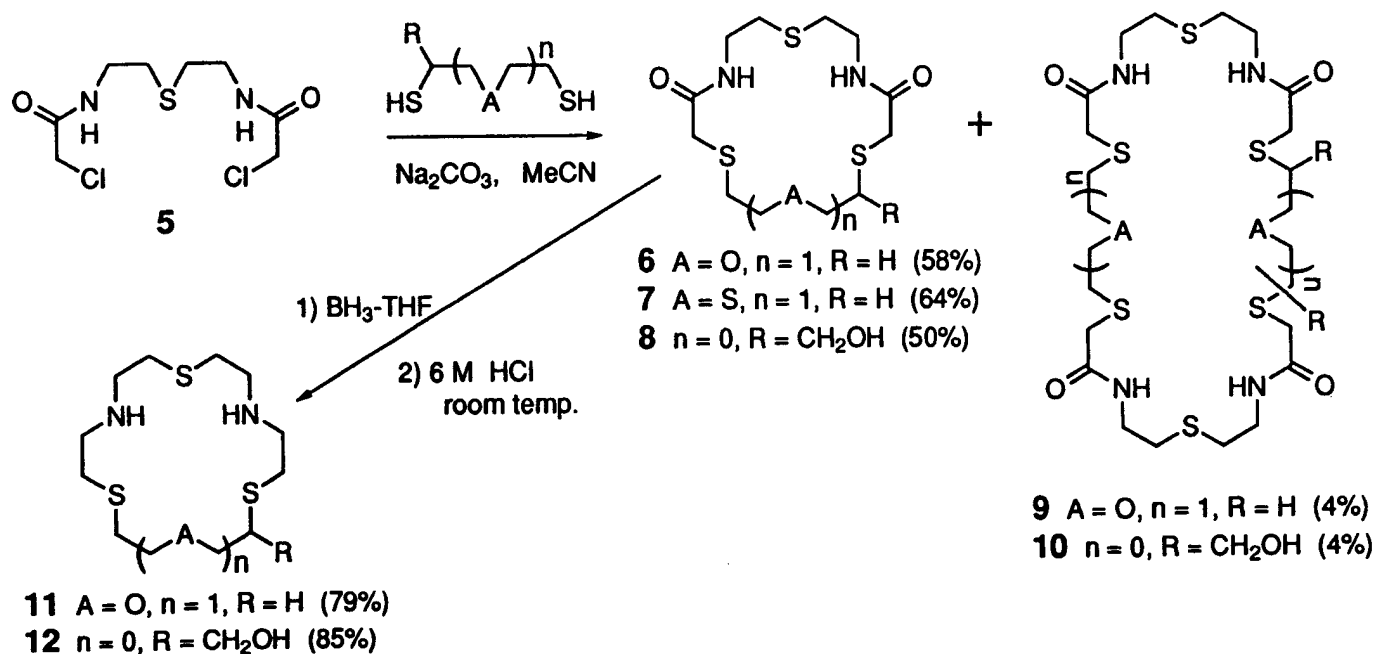
Synthesis of 8-Hydroxyquinoline-substituted Ligands. Ligands **14-16** with the CHQ units attached at the CHQ 7-position were formed using Mannich reaction conditions as shown in Scheme 3.^{1d,3} The best results were achieved by first forming the *N,N'*-bis(methoxymethyl)diazacrown ethers by stirring the diaza crowns in methanol and a slight excess of paraformaldehyde.³ After removal of methanol and addition of benzene to the mixtures, CHQ was added and the mixtures were refluxed. Benzene

proved to be a good reaction solvent since there were few side products. Products **14-16** were purified using radial chromatography.

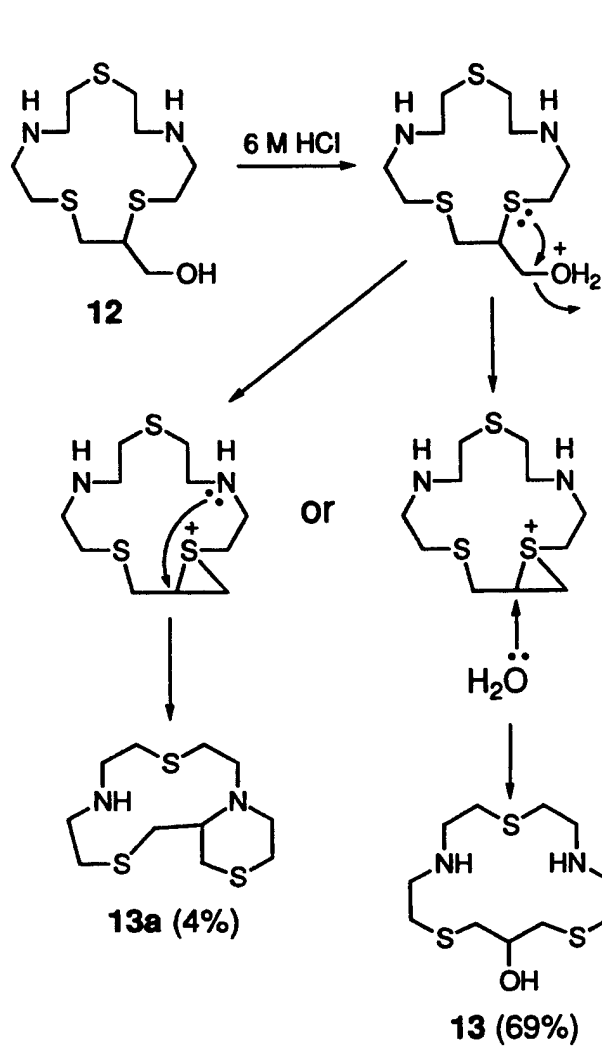
Compounds **17-19** (Scheme 4) were obtained in good yields using a reductive amination procedure.^{1a,1b} Ligands **17-19** with the 8-hydroxyquinoline side arms attached at their 2-positions were more readily isolated than compounds **14-16** with CHQ units attached at their 7-positions.

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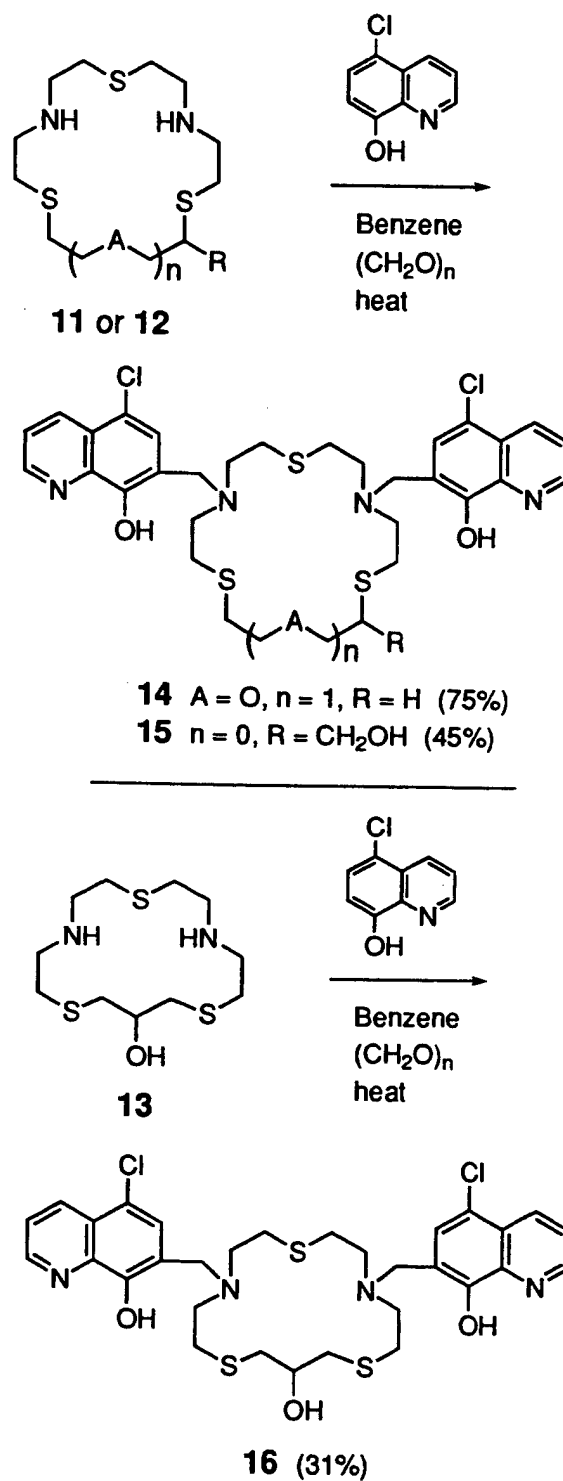
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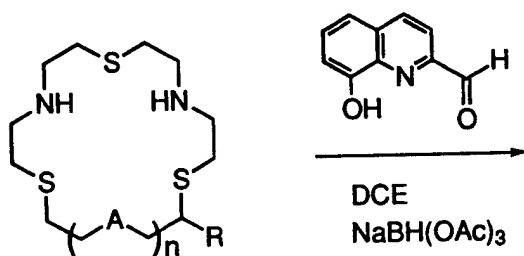
Scheme 1. Syntheses of diazatrithiacrown ethers **11** and **12** containing two unsubstituted nitrogen atoms



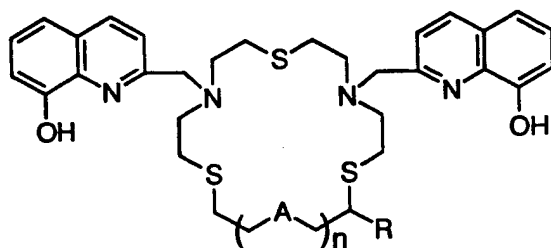
Scheme 2. Rearranged crown ethers **13** and **13a**



Scheme 3. Syntheses of 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted crown ethers via the Mannich reaction

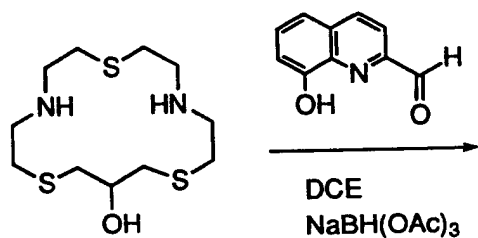


11 or 12

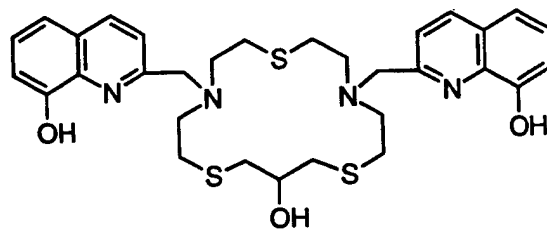


17 A = O, n = 1, R = H (75%)

18 n = 0, R = CH₂OH (69%)



13



19 (64%)

Scheme 4. Syntheses of 8-hydroxy-quinolin-2-ylmethyl-substituted crown ethers via reductive amination